a receptor for advanced glycation endproduct (RAGE) in a competitive assay using a peptide that is a carboxymethyl-lysine-modified AGE, does not reasonably provide enablement for a peptide derivative comprising an **alkyl group** [emphasis added]. The Examiner stated that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

In response, applicants respectfully traverse the Examiner's above rejection. Contrary to the Examiner's above statement, **a carboxymethyl-lysine (hereafter CML) modified AGE is an alkyl derivative of AGE that binds RAGE.** Accordingly, the present invention is enabled for the use of a peptide comprising an alkyl derivative in the assay as claimed.

Applicants attach hereto as **Exhibit B**, a copy of the International Union of Pure and Applied Chemistry(IUPAC)Compendium of Chemical Terminology which recites that alkyl groups are "univalent groups derived from *alkanes* by removal of a hydrogen atom from any carbon atom $-C_nH_{2n+1}$." Therefore, the IUPAC Compendium of Chemical Terminology defines the chemical structure of the **methyl** group of CML-modified AGE, i.e. $-NH\mathbf{CH}[(CH_2)_4NHCH_2CO_2^-]C(O)-$, as an alkyl group. Accordingly, applicants contend that a CML-modified AGE is an alkyl derivative of AGE which binds RAGE. Therefore, claims 11-12 are enabled.

Claim 29

The Examiner maintained the rejection of claim 29 alleging that the specification is not enabling of the method claimed, for reasons of record in the previous Office Action, Paper No. 11, at pages 4-5.

The Examiner stated that applicant traverses and asserts on page 8 of the amendment that one skilled the art of competition assays for determining whether a compound is capable of inhibiting the interaction of a peptide with a receptor for advanced glycation end product (RAGE) would understand the specification on page 9, lines 34 and 35, "In another embodiment of the screening method, the admixing of step (a) occurs in a cell," to be sufficiently enabling to carry-out in vitro experiments when viewed in light of page 9, line 20, i.e. "the screening method may be carried out in vitro,....., or wherein the components in step a are admixed inside of a cell." The Examiner stated that applicants contend that these comments obviate the above rejection. The Examiner stated that applicant's arguments have been considered but are not persuasive. The Examiner stated that althought these statements are present in the specification as indicated, the statements themselves are not enabling of the method. The Examiner alleged that the specification or the prior art has not provided the person of ordinary skill in the art the guidance necessary to be able to use the peptide comprising an alkyl derivative in the assay as claimed. The Examiner stated that an additional literature search by the Examiner failed to discover a single instance in which a competitive binding assay as described in claim 1 is performed

inside a cell. The Examiner stated that the rejection under 35 U.S.C. §112, first paragraph is maintained.

In response, applicants respectfully traverse the Examiner's above rejection. Nevertheless, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have hereinabove amended claim 29 to more clearly describe the presently claimed invention. Claim 29 now recites as follows: "The method of claim 1, wherein step (a) occurs *in vitro* or *in vivo*." Therefore, claim 29 no longer recites the alleged limitation "in a cell." Accordingly, applicants contend that amended claim 29 obviates the Examiner's above rejection and request that the Examiner reconsider and withdraw this ground of rejection.

Rejection under - 35 USC § 102(e)

The Examiner maintained the rejection of claims 1, 2, 5-8, 13, 15, 17, 18, 20-22 and 24-28 under 35 U.S.C. 102(e) as allegedly being anticipated by Morser et al., U.S. patent No. 5,864,018, filed April 16, 1996, for reasons cited in the previous Office Action, Paper Nos. 9 and 11.

The Examiner stated that applicants traverse the rejection and maintain that Morser et al. does not disclose every limitation of applicants claimed invention for reasons cited in the previous response to July 10, 2001 Office Action, at pages 11 and 12, and applicants contend that these comments obviate the above rejection.

The Examiner stated that applicants comments have been considered but are not persuasive. The Examiner alleged that applicants arguments were addressed in the previous Office Action, Paper No. 11 at pages 6-7, and as no new arguments have been set forth, the reasons for the rejection are maintained.

In response, applicants respectfully traverse the Examiner's rejection. Applicants contend that the claimed invention is distinguishable from Morser et al. Applicants contend that Morser et al. fail to disclose or claim any carboxymethyl-lysine(CML) modified AGE, a distinguishable moeity from the standard AGE-BSA disclosed in Morser et al. Accordingly, Morser et al. does not anticipate each and every element of the applicants' claimed invention.

In support, the specification recites that AGEs are a "modified class of compounds that result from the process of glycoxidation." See page 28, lines 8-9. Further, the specification recites that " in order to determine which ones of known AGE structures interact with RAGE, we prepared a series of synthetic AGEs and tested their ability to interact with RAGE." See page 28, lines 17-20. The specification goes on to recite that the "infusion of CML-modified BSA, but not native protein, into normal mice increased mRNA for VCAM-1 in the lung," and that these studies "identify CML-modified structures and v-domain of RAGE as a critical target for the design of agents to block the development of cellular perturbation, and, perhaps the complications of the vasculature and inflammatory cells

that characterize disorders of AGE(CML) accumulation." See page 28 line 35 and page 29, lines 1-11. Therefore, the specification recites that CML-modified proteins are a specific subset of AGEs which interact with RAGE.

In contrast, Morser et al. do not claim or disclose any use of CML-modified peptides. Morser et al. recite that "the screening methods of the present invention typically involve the incubation of a polypeptide of the present invention, e.g., a soluble human RAGE polypeptide, in the presence of a **standard advanced glycosylation end-product protein (AGE) such as AGE-BSA**, nonenzymatically N-glycosylated collagen, myelin or the like, as well as the test compound."[Emphasis added] See column 16, lines 50-54. Therefore, Morser et al. fail to claim or disclose any CML-modified peptides.

Accordingly, applicants contend that because Morser et al. merely describe a standard advanced glycosylation end-product protein (AGE) and do not disclose or claim the **CML-modified AGE** of the present invention, it does not anticipate each and every element of the applicants' presently claimed invention.

Rejection under - 35 U.S.C. §103(a)

The Examiner stated that claim 4 remains rejected under 35 U.S.C. §103(a) as being unpatentable over Morser et al., as applied to claims 1,2,5-8,13,15,17,18,20-22 and 24-28 and further in view of Reddy et al., for reasons cited in the previous Office Actions,

Paper Nos. 9 and 11.

The Examiner stated that applicants' traverse the rejection and assert that the mere fact that references can be combined does not make the resultant combination obvious unless the prior art also suggests the desirability of the combination. The Examiner stated that applicants contend that the prior art does not suggest the desirability of the combination of Reddy et al. and Morser et al. when viewed well within the ordinary skill of the art at the time the claim was made. The Examiner stated that applicants contend that the Examiner used impermissible hindsight when combining Morser et al. and Reddy et al. to demonstrate prima facie obviousness in claim 4. The Examiner stated that the applicants argue that while Reddy et al. teaches that carboxy-methyl-lysine-modified peptides are a dominant AGE, it would not have been prima facie obvious to one skilled in the art of AGE/RAGE art at the time of the invention touse a carboxymethyl-lysine-modified peptide of Reddy et al. as the AGE in the AGE/RAGE competition assay of Morser et al. The Examiner stated that applicants further point out that Reddy et al. demonstrates antigenic dominance of the N-(Carboxymethyl)lysine form of AGE in tissue proteins, not the specificity of its binding to RAGE, and that Lander et al. and Yan et al. demonstrate a complex experimental landscape of heterogeneous AGE/RAGE interactions mediated by oxidant stress. The Examiner alleged that applicants assert that combining knowledge of antigenic dominance of a particular peptide with knowledge of the state of the work within a field of complex

heterogeneous AGEs does not necessarily enable one of ordinary skill in the art to determine AGE/RAGE binding efficiency. The Examiner stated that applicants contend that these comments obviate the rejection.

The Examiner stated that applicants' comment have been considered but are not persuasive. The Examiner stated that in response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. The Examiner stated that so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See In re McLaughlin, 443 F. 2d 1392, 170 USPQ 209 (CCPA 1971).

The Examiner alleged that since Reddy et al. demonstrated that carboxymethyl-lysine was a dominant form of AGE at the time of the invention, it would have been prima facie obvious for one of ordinary skill at that time of the invention to use modified carboxymethyl-lysine peptides in the AGE/RAGE assay, because an "AGE" is defined as a compound that binds to a receptor for an AGE. The Examiner Stated therefore, the rejection under of 35 U.S.C. 103 is maintained.

In response, applicants respectfully traverse the Examiner's above

argument and contend that the cited references, namely Morser et al., U.S. Patent No. 5,864,018 ("'018 patent")in view of Reddy et al., Biochemistry, 1995; 34(34)10872-76; ("Reddy paper") do not render obvious applicants claimed invention. Contrary to the Examiner's assertion that an "AGE" is defined as a compound that binds to a receptor for an AGE, all AGES **do not** bind RAGE, which is supported by the Declaration under 37 C.F.R. §1.132 of Ann Marie Schmidt attached hereto as **Exhibit C** and the specification of the above-identified application. Specifically, it was not known as of October 5, 1998 (i.e. the earliest date priority of which is claimed in the present invention) which AGEs as part of a heterogeneous group of compounds might bind to RAGE or of the importance of such adducts biologically.

Declaration of Ann Marie Schmidt under 37 C.F.R. §1.132

The Declaration of Ann Marie Schmidt, attached hereto as Exhibit C, establishes the following:

1. A screening method for determining whether an advanced glycation endproduct (AGE) binds to receptor for advanced glycation endproduct (RAGE) is purportedly described in the screening applications of the '018 patent.

2. The Reddy paper purportedly describes that a particular AGE, the CML-adduct, might be an antigenic dominant form of AGE *in vivo*.

3. The common understanding in the field as of October 5, 1998 (i.e. the earliest date priority of which is claimed in the present invention) was that AGEs are a heterogeneous group of compounds and that CML-AGE might be a dominant AGE found *in vivo*. The Reddy paper provided a potentially quantitative *in vivo* assessment of N$^{\varepsilon}$-(Carboxymethyl)lysine but failed to provide any insight into the potential binding of any AGE adducts to RAGE or of the importance of such adducts biologically.

4. Ann Marie Schmidt directed and supervised experiments to make many AGE adducts in order to test for binding to RAGE. The results of these experiements demonstrated that not all AGE adducts bind to RAGE.

5. As of October 5, 1998, there was no reasonable expectation of success that a CML-AGE adduct would preferentially bind RAGE.

Applicants claimed invention provides an unexpected result

The present invention recite in part "a method for determining whether a compound is capable of inhibiting the interaction of a peptide with a receptor for advanced glycation end product (RAGE)" wherein "the peptide is a **carboxymethyl-lysine-modified AGE**" [emphasis added].

The '018 patent recites a method of identifying effectors of AGE/RAGE interaction using "a soluble human RAGE polypeptide, in the presence of a **standard advanced glycosylation end-product protein (AGE)** such as AGE-BSA" [emphasis added]. Therefore, the '018 patent fails to disclose any use of a CML-AGE in the method of screening for effectors of AGE/RAGE interaction.

The Reddy paper recites that "N$^{\varepsilon}$-(Carboxymethyl)lysine is a dominant advanced glycation end product (AGE) antigen in tissue proteins." Therefore, while the Reddy paper may at most disclose that N$^{\varepsilon}$-(Carboxymethyl)lysine is a dominant advanced glycation end product (AGE) antigen in tissue proteins thereby giving a potentially quantitative assessment of CML-AGE *in vivo*, it fails to provide any insight into the potential binding of CML to RAGE or the importance of the adduct biologically. Therefore, as described above, at the time that the present application was filed, one skilled in the art would not have expected that the CML adduct of the Reddy paper would preferentially bind RAGE while other common AGEs such as pentosidine and methylglyoxal would fail to bind RAGE. Therefore, it would not have been obvious to determine whether a compound is capable of inhibiting the interaction of a carboxymethyl-lysine-modified AGE peptide with a receptor for advanced glycation end product (RAGE) since it was neither known nor expected that CML adduct would preferentially bind RAGE.

Accordingly, as described above, Ann Marie Schmidt directed and supervised experiments to make many AGE adducts in order to test

for binding to RAGE. These experiments demonstrate that two common AGEs, pentosidine and ethylglyoxal, **did not** bind RAGE while one AGE, the CML adduct, did bind RAGE. This was a surprising result since previously it had been neither known nor expected that the CML adduct would preferentially bind RAGE.

Since there was no disclosure as of October 5, 1998, i.e. the earliest date of which priority is claimed in the present application, regarding the binding of CML-AGE to RAGE, it was unexpected that a CML-AGE would preferentially bind RAGE while other common AGES, i.e. pentosidine and methylglyoxal, would fail to bind RAGE. Accordingly, applicants' claimed invention provides an unexpected result over the '018 patent further in view of the Reddy paper and it would **not** have been prima facie obvious for one of ordinary skill at that time of the invention to use modified carboxymethyl-lysine peptides in the AGE/RAGE assay. Applicants contend that these remarks obviate the above rejection and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

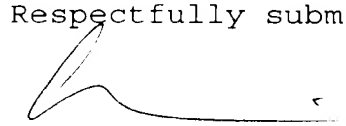
Summary

For the reasons set forth hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the various grounds of objection and rejection and earnestly solicit allowance of the now pending claims, i.e. claims 1, 2, 4-8, 11-13, 15, 17, 18, 20-22 and 24-29.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone either of them at the number provided below.

No fee, other than the enclosed $460.00 fee for a three-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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I hereby certify that this correspondence is being deposited this date with the U.S. postal Service with sufficient postage as first class mail in an envelope addressed to:

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Washington, DC 20231

6/19/02

Alan J. Morrison — Date
Reg. No. 37,399

Exhibit A

--29. (Amended) The method of claim 1, wherein step (a) occurs [in a cell] *in vitro* or *in vivo*.--

alkyl groups

Univalent groups derived from *alkanes* by removal of a hydrogen atom from any carbon atom $-C_nH_{2n+1}$. The groups derived by removal of a hydrogen atom from a terminal carbon atom of unbranched alkanes form a subclass of normal alkyl (*n*-alkyl) groups $H[CH_2]_n$. The groups RCH_2, R_2CH ($R \neq H$), and R_3C ($R \neq H$) are primary, secondary and tertiary alkyl groups, respectively.

See also *cycloalkyl groups*, *hydrocarbyl groups*.

1995, *67*, 1314